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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,049	01/17/2006	Kristen E. Belmonte	PU60400	6150

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EXAMINER	
O DELL, DAVID K	
ART UNIT	**PAPER NUMBER**
1609	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/09/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,049	BELMONTE ET AL.	
	Examiner	Art Unit	
	David K. O'Dell, Ph.D.	1609	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2006*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☑ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-13 are pending in the application.

2. This application is a national stage of PCT/US2004/023042 filed on July 16, 2004 which claims priority to U.S. Provisional Application No. 60/488,061 filed July 17, 2003.

Specification

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Since applicant has 7 copending applications (10/565,048, 10/523,478, 10/552,492, 10/565,046, 10/575,837, 10/575,839, 11/568,909) with the same title, confusion may arise. The following title is suggested: 2'-2'-Substituted-3-Ethyl-Tropane Salt Muscarinic Acetylcholine Receptor Antagonists and Compositions.

Abstract

4. Applicant is reminded of the proper content of an Abstract of the Disclosure. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. A description of the compounds such as "2'-2'-Substituted-3-Ethyl-Tropane Salts" followed by the

already present claimed use would be sufficient. Complete revision of the content of the abstract is required on a separate sheet.

Claim Rejections – 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Zirkle et. al. *Journal of Medicinal & Pharmaceutical Chemistry*, **1962**, *5*, 341-356. Zirkle teaches the compounds of the current invention. In this publication the compound of claim 3 (3-endo)-3-(2,2-diphenylethyl)-8,8-dimethyl-8-azoniabicyclo[3.2.1]octane bromide (applicant's name), Registry #: 106655-97-4 is synthesized and evaluated for its anticholinergic activity. This MeBr salt is listed in "Table IV" as "No. c" "mp 257-258". Claims 1-2, & 4 are of course anticipated by this compound.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 5-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to the following:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)

(A) The breadth of the claims: The claims are broad and drawn to many respiratory conditions, but that's not really the main concern here. **(B) The nature of the invention:** This invention is drawn towards a method for treating diseases. **(D) The level of one of ordinary skill:** One of ordinary skill in the art of treating diseases or determining which drug to use for the treatment of a condition would be either a medical doctor or Pharm D. **(C) The state of the prior art:** While Zirkle states that these compounds are the preferred compounds of his study, and effective *in vitro* as anti-cholinergics (ibid., pg. 352-353), we don't know how these compounds behave *in vivo*. **(F) The amount of direction provided by the inventor and (G) the existence of working examples:** While the applicant has provided descriptions of assays in the

specification, and statements like "All data is given as mean +- standard error of the mean..."(pg. 7), the examiner cannot find the data in the specification. Statements like the one found on pg 9 line 14 "This experiment allows for the determination of duration of activity of the administered compound..." without actually providing a single piece of data lead the examiner to believe that these are mere recitations of possible experiments that could be performed with the compounds and that none were actually performed. No working examples exist. **(E) The level of predictability in the art and (H) the quantity of experimentation needed to make or use the invention:** In the absence of this data we are left with an old compound that is an anticholinergic, however it is well known that there are many muscarinic receptor sub-types and even before the application was filed a review article (Lee, A.M. et. al. *Current Opinion in Pharmacology* **2001**, *1*, 223-229) tells us that at least five distinct subtypes of muscarinic receptor exist (M1-M5 in humans). Each one of these GPCRs has distinct tissue distribution, second-messengers and most-importantly ligand profile. All that we currently know about these compounds is that they inhibit the action of acetylcholine in a non-specific assay (given in 1962 the subtypes of muscarinic receptors were not known). Maybe these were organ bath assays with sheep vas deferens, pig heart or guinea pig ileum. We don't know, but it would be helpful to know the tissue type and animal. Even if we know the tissue type these receptors are of course GPCRs and the differences between the animal protein and those found in humans is sometimes substantial (more or less subtypes, or little homology). What creatures will be treated with these compounds? It was well known at the time of the invention that in order to be

used in applicants claimed manner (a disease, and specifically a lung disease like COPD and asthma, claims 7-12), that the sub-type selectivity is very significant parameter to be determined in assessing the *potential* therapeutic benefit of a putative pharmaceutical. Lee, A.M. et. al. ibid. state on pg. 225:

> Nonselective muscarinic receptor antagonists
> Atropine, ipratropium and oxitropium are nonselective antimuscarinic drugs that successfully abrogate bronchoconstriction and airway hyperreactivity in humans; however, they bind M2 and M3 muscarinic receptors with equal affinity [5]. Since the M2 subtype is an inhibitory prejunctional autoreceptor, blocking the M2 muscarinic receptor with a nonselective antagonist increases acetylcholine release and **may enhance bronchoconstriction.**
> Ipratropium (Boehringer Ingelheim Pharmaceuticals Inc., California, USA) is the most widely used anticholinergic medication for airway disease. In guinea pigs, although it prevents bronchoconstriction in doses above 10 μg/kg (intravenous), it doubles vagally stimulated bronchoconstriction at lower doses. [48]. Paradoxical bronchoconstriction to ipratropium has been reported in humans [49,50], although no systematic study of M2 receptor blockade has been performed. Thus, the clinical efficacy of anticholinergics probably depends on the balance between M2 and M3 muscarinic receptor antagonism.

Thus we need to know several things: 1) Do these compounds antagonize muscarinic receptor subtypes found in the lungs? 2) What is the selectivity for receptor subtypes? 3) Are the effects *in vitro* correlated with *in vivo* activity? Number three is perhaps the most important factor, given the complexity of receptor sub-types, the possibly different affinities, rates of dissociation, etc. The real question is does it work as a therapy in a creature? Again it must be reiterated that applicant has provided absolutely no data for these compounds, although Smith-Kline French may have acquired such data, it has

apparently not been published. Since no data is given we cannot begin to evaluate these compounds as drugs, hence any claim directed towards inhalant formulations cannot be evaluated. It is also noted that no such formulations have been prepared and applicant has simply listed a laundry list of possibilities. We are provided with no answers to the questions above, thus it is very clear that one could not use this invention that has no working examples in this unpredictable art without undue experimentation.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David K. O'Dell, Ph.D. whose telephone number is (571) 272-9071. The examiner can normally be reached on Mon-Fri 7:30 A.M.-5:00 P.M EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

D.K.O.

Cecilia Tsang
CECILIA TSANG
SUPERVISORY PATENT EXAMINER